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Synthesis of the Hydrazines

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The series of compounds derived from hydrazine (diamide), NH_2-NH_2, is termed generally "the hydrazines." Any or all of the hydrogen atoms of the parent compound may be substituted.

The hydrazines may be classified in several ways. Sidgwick, indicating the two nitrogen atoms as N and N′, divides the derivatives of hydrazine into the following classes:

1. Those which contain an -NH_2 group; i.e., the monosubstituted hydrazines, and the unsymmetrical or N,N-disubstituted hydrazines.
2. The symmetrical or N, N′-disubstituted hydrazines, also called hydrazo (hydrazi-) compounds.
3. The tri- and tetra-substituted compounds.
4. The hydrazones and azines.
5. The acyl derivatives of hydrazine (the hydrazides and hydrazidines).

Groups 4 and 5 of the above classification will not be considered in this review.

The aromatic hydrazines, used as starting intermediates for the preparation of certain heterocyclics and as reagents suitable for the identification of carbonyl compounds, are much more important than the corresponding alkyl hydrazines.

The methods for the preparation of the hydrazines are related in part to those for the preparation of the amines. The monosubstituted hydrazines may be prepared:

1. By the substitution or exchange of one of the hydrogen atoms of hydrazine.

a. Reaction with organic halides.

This reaction is very limited in the aliphatic series. Westphal has reported the formation of alkyl hydrazines by this method. In the aromatic series the exchange of halogen for the hydrazino group proceeds readily if the halogen is activated, especially by nitro groups. 2,4-Dinitrophenylhydrazine is prepared in 81-85% yield as follows:

$$C_6H_3(NO_2)_2Cl + NH_2NH_2 \cdot H_2SO_4 \xrightarrow{KOAc} C_6H_3(NO_2)_2NHNH_2$$

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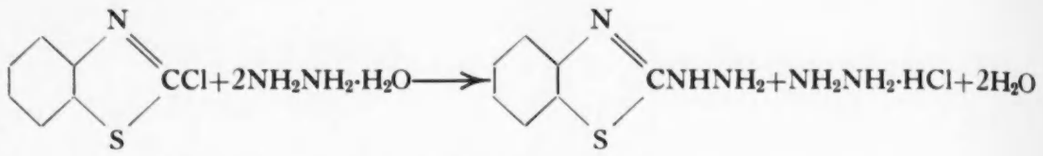
Heterocyclic hydrazines are prepared similarly. This modification may be illustrated by the formation of 2-benzothiazolylhydrazine. The yield is 92% of the theoretical.



b. Reaction with salts of alkyl hydrogen sulfates.

$$ROSO_2OK + 2H_2NNH_2 \longrightarrow RNHNH_2 + KOSO_2OH \cdot N_2H_4$$

c. Reaction with an aldehyde, methylation of the corresponding hydrazone, and subsequent hydrolysis. Methylhydrazine sulfate is prepared in 51-54% yield by this procedure.

$$2C_6H_5CHO + NH_2NH_2 \cdot H_2SO_4 \xrightarrow{(NH_3)} C_6H_5CH{=}N{-}N{=}CHC_6H_5$$

$$\xrightarrow[3H_2O]{(CH_3)_2SO_4} 2C_6H_5CHO + CH_3NHNH_2 \cdot H_2SO_4 + CH_3OH$$

d. By the reaction with naphthols.

$$C_{10}H_7OH + NH_2NH_2 \xrightarrow{heat} C_{10}H_7NHNH_2$$

e. By a Hofmann-type reaction.

$$RNHCONH_2 + NaOBr \xrightarrow{NaOH} RNHNH_2 + NaBr + CO_2$$

f. From a bromo-amine by the method of Kijner.

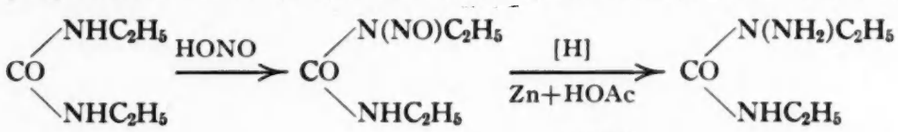
$$2RR'CH \cdot NH_2 \xrightarrow{2NaOBr} 2RR'CH \cdot NHBr \xrightarrow{Ag_2O} RR'CHN{=}NCHRR'$$

$$\xrightarrow{\text{rearranges}} RR'C{=}NNHCHRR' \xrightarrow{\text{hydrolysis}} RR'CHNHNH_2 + RR'CO.$$

2. *By reduction methods.*

a. Acid reductions.

(1) E. Fischer's method for the reduction of nitrosoalkylurea derivatives is most suitable for the aliphatic series. It is probably the best method for the preparation of ethylhydrazine, the yield being 47% of the theoretical.



$$\xrightarrow[HCl]{H_2O} C_2H_5NHNH_2 \cdot HCl + C_2H_5NH_2 \cdot HCl + CO_2.$$

(2) Victor Meyer's method, in which a diazonium salt solution is reduced directly to the hydrazine with stannous chloride, is widely used in the aromatic series, usually with 60-80% yields.

$$ArN_2Cl + 2SnCl_2 + 4HCl \longrightarrow ArNHNH_2 \cdot HCl + 2SnCl_4$$

(3) The action of zinc diethyl on benzenediazonium chloride suspended in dry ether is reported to result in α,β-diethylphenylhydrazine as the principal product.

b. Alkaline reductions.

(1) The alkaline reduction of diazonium compounds was developed by

E. Fischer. The preparation of phenylhydrazine in 80-84% yield is a well-known example.

$$C_6H_5NH_2\cdot HCl \xrightarrow{HONO} C_6H_5N_2Cl \xrightarrow{Na_2SO_3} C_6H_5N{=}NSO_3Na$$

$$\xrightarrow[\text{and hydrolysis}]{\text{reduction}} C_6H_5NHNH_2\cdot HCl \xrightarrow{NaOH} C_6H_5NH\cdot NH_2.$$

The reduction step has been carried out both with acid and alkaline reagents. Zinc and acetic acid, sulfurous acid, and sodium hydrosulfite have been used. One method that has been used indicates that an excess of sodium sulfite is all that is needed, at least for this particular case.

(2) In caustic alkaline solutions, the metallic diazotates may be reduced by sodium amalgam.

(3) Hydrazine derivatives have been prepared by the use of sodium stannite. Normally the hydrocarbon is formed with loss of nitrogen when this agent is used. It has been postulated that the reduction proceeds through the intermediate phenyldiimide, $C_6H_5N{=}NH$, which is unknown. Addition of sodium benzenediazotate to sodium stannite with alcohol and benzaldehyde, results in benzoylphenylhydrazine. The reaction is explained as the condensation of the intermediate diimide and the aldehyde:

$$C_6H_5N{=}NH + C_6H_5CHO \longrightarrow C_6H_5NHNHCOC_6H_5.$$

The unsymmetrical disubstituted hydrazines may be prepared by the reduction of secondary nitrosoamines. This method may be used in the preparation of alkyl hydrazines such as unsym.-dimethylhydrazine hydrochloride in 69-73% yield, mixed alkyl-aryl hydrazines such as α-methyl-α-phenylhydrazine in 52-56% yield, or aryl hydrazines such as α,α-diphenylhydrazine in 32% yield.

$$(C_6H_5)_2NNO \xrightarrow[Zn+HOAc]{[H]} (C_6H_5)_2NNH_2$$

The symmetrical disubstituted hydrazines may be prepared:

1. Indirectly by the use of a dihydrazide.

The hydrazine is converted to the diformyl or the dibenzoyl derivative. The acyl groups are removed by hydrolysis after methylation. The yield is 75-78% of the theoretical.

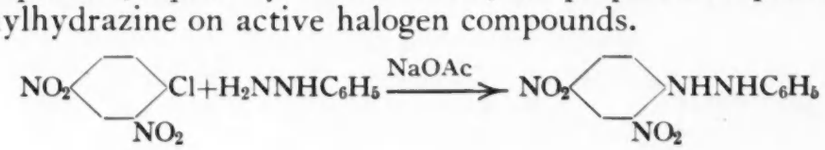
$$2C_6H_5COCl + NH_2NH_2\cdot H_2SO_4 \xrightarrow{NaOH} C_6H_5CONHNHCOC_6H_5$$

$$\xrightarrow[2NaOH]{2(CH_3)_2SO_4} C_6H_5CON(CH_3)N(CH_3)COC_6H_5 \xrightarrow[2H_2O]{2HCl} CH_3NHNHCH_3 + 2C_6H_5COOH.$$

2. By the reduction of nitro and azo compounds, either electrolytically or with zinc dust and alcoholic potassium hydroxide.

$$2C_6H_5NO_2 \xrightarrow{[H]} C_6H_5NHNHC_6H_5$$

Hydrazo compounds, especially nitrated ones, are prepared frequently by the action of phenylhydrazine on active halogen compounds.



The trisubstituted hydrazines are difficult to prepare and have been little investigated. The only method of preparation of value is as follows:

$$C_6H_5NNO \xrightarrow{R'MgBr} C_6H_5NN\text{-}OMgBr \xrightarrow[\text{and reduction}]{\text{hydrolysis}} C_6H_5NNH$$
$$\quad\;\; | \qquad\qquad\quad || \qquad\qquad\qquad\quad || \qquad\quad$$
$$\quad\;\; R \qquad\qquad\quad RR' \qquad\qquad\qquad\quad RR'$$

Tetrarylhydrazines may be obtained by dehydrogenation of diaryl amines. Tetraphenylhydrazine may be prepared as follows:

$$2(C_6H_5)_2NH \xrightarrow[KMnO_4]{[O]} (C_6H_5)_2NN(C_6H_5)_2.$$

Reagent to Identify Carbonyl Compounds

N-Methyl-β-carbohydrazidopyridinium *p*-toluenesulfonate* is an excellent reagent for use in the identification of carbonyl compounds. Its use furnishes solid derivatives that have melting points in a convenient range. The substances are obtained in a good yield and are easily purified; they are soluble in water. The reagent can be used to form derivatives with halogenated carbonyl compounds as well as with ordinary aldehydes, ketones, and the like.

A further advantage of this reagent is that the derivatives formed by its use can be recovered by a short hydrolysis. A novel application of this fact makes it possible to prepare two derivatives with the same specimen; it is not necessary to perform a separate operation, for the hydrolysis takes place in the acidic solution of the second reagent, for example, 2,4-dinitrophenylhydrazine.

The melting points of a large number of derivatives are given in the *Journal of Organic Chemistry*, **6**, 596-601 (1941).

*Eastman Organic Chemical No. 5268. For brevity, the reagent has been called "nictazine" and its derivatives, "nictazones."

New Eastman Organic Chemicals

NOTE: Over 75 additions to the list of Eastman Organic Chemicals are enumerated in an Eastman Kodak Company advertisement appearing in the October 17, 1949 issue of *Chemical & Engineering News*. Below are a few of them.

6144	iso-Butyraldoxime BP 141-143°	10 g.	$1.50 B
	$(CH_3)_2CHCH{:}NOH$ . . . MW 87.12		
6178	iso-Butyryl Bromide BP 114-116°	100 g.	6.00 C
	$(CH_3)_2CHCOBr$ . . . MW 151.01		
6184	2,5-Dichlorophenyl Isocyanate BP 118-119°/18mm	100 g.	6.00 C
	$Cl_2C_6H_3NCO$ . . . MW 188.02		
6138	Diethylacetyl Chloride BP 137-139°/15 mm	100 g.	3.00 C
	$(C_2H_5)_2CHCOCl$ . . . MW 134.61		
6195	β-3,4-Dimethoxyphenylethylamine BP 163-165°/14 mm	100 g.	9.00 C
	$(CH_3O)_2C_6H_3CH_2CH_2NH_2$ . . . MW 181.23		
6210	2-Hydroxy-5-bromobenzaldehyde MP 106-108°	100 g.	8.50 C
	HOC_6H_3BrCHO . . . MW 201.03		
6147	2-Nitro-1,3-dimethylbenzene MP 13-15°	500 g.	3.50 D
	$NO_2C_6H_3(CH_3)_2$ . . . MW 151.16		
6142	Trimethylene Iodide BP 109-111°/23 mm	100 g.	6.00 C
	$I(CH_2)_3I$ . . . MW 295.92		